Review Paper

Neonatal Exposure to Drugs in Breast Milk

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There are many benefits of breast-feeding both for the infant and for the mother. Nursing mothers who are also taking medications or exposed to environmental hazards may be confronted with a difficult choice to discontinue nursing or maternal medication or risk potential harm to the infant. Frequently, these decisions are made without sufficient information or understanding of the factors influencing exposure. The current review explores two indices of exposure, together with their pharmacokinetic determinants. Both of the indices include the milk to serum (M/S) concentration ratio for a given drug and the volume of milk consumed. The first exposure term, $EI_{(Dose)}$, expresses neonatal dose as a percentage of maternal dose and is inversely related to the maternal systemic clearance. By contrast, the second exposure term, $EI_{(Conc)}$, expresses infant concentration as a percentage of maternal concentration and is inversely related to the infant systemic clearance. Issues related to intersubject variation in M/S (e.g., colostrum vs. mature milk, fore vs. hind milk) and infant clearance (e.g., ontogeny of elimination pathways, pharmacogenetics) and their role in modulating exposure are also discussed.

KEY WORDS: breast-feeding, infant exposure, nursing, pharmacokinetics, risk assessment.

INTRODUCTION

Concern over drug transfer into human milk is the result of a major trend during the last 40 years to return to breast-feeding for infant nutrition. In 1992, 52% of infants at 1 week of age were receiving breast milk in the United States (1,2). The return to breast-feeding has been motivated principally by the multiple and unique advantages of human breast milk (3–5): maternal–infant bonding; lower incidence of infant morbidity; bactericidal effect of lysoenzyme; presence of immunoglobulins and complement; better iron absorption; less obesity; and lower food allergy incidence. Recently, Mortensen *et al.* (6) found a positive association between duration of breast-feeding and intelligence using two different intelligence tests. There is also evidence of benefit for the mother with the risk for premenopausal breast cancer reduced with lactation and that effect is magnified for women who had extended periods of breast-feeding (7). In the face of these beneficial aspects of breast-feeding, the presence of drugs and other harmful agents has arisen as a significant negative consideration in the decision to breast-feed (8). Greater than 90% of women take at least one medication during the first week following delivery (9,10). Drug utilization surveys have indicated that 17% of the mothers who were still breast-feeding at 4 months had taken at least the equivalent of one daily dose of one drug. In addition, 5% of the mothers who continued to breast-feed were receiving medication for chronic conditions such as asthma, allergy, hypertension, arthritis, diabetes, and epilepsy or migraine (9).

To facilitate a decision regarding breast-feeding in the case where the mother is taking medications, several issues need to be addressed (11–14):

- What is the maternal therapy?
- Is the drug selection therapeutically sound?
- Does it involve acute or chronic therapy?
- What is the consequence of the mother forgoing therapy?
- Are there alternatives and have these been proven safe for the neonate?
- What are the risks to the newborn?
- What are the pharmacological/toxicological mechanism(s) of action?
- What is the amount of the dose exposure?
- Is the ability of the newborn to eliminate the drug impaired?
- Are there any physiological or biochemical reasons to believe the newborn to be more susceptible to the effects of the drug?

The goal of this article is to explore the derivation and use of indices as a tool for assessing infant exposure. Hypothetical and real examples are used to illustrate the impact of various pharmacokinetic and physiological parameters on these exposure indices as well as sources of intersubject variability.

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ABBREVIATIONS: C_{max}, peak serum drug concentration; $\overline{C}$, average serum concentration of drug at steady state; $Cl_{systemic}$, systemic clearance; $EI_{(Conc)}$, exposure index related to maternal concentration; $EI_{(Dose)}$, exposure index related to maternal dose; F, bioavailability; M/S, milk to serum ratio; V_{milk}/τ, volume of milk consumed per nursing interval (or per day).

EXPOSURE INDEX

Systemic Exposure

It is highly likely that all maternally administered drugs and environmental chemicals will find their way into the breast-feeding infant (14–19). An exception to this may be large-molecular-weight compounds (e.g., proteins); however this principle has not been well tested. In order to establish the safety or hazard of drugs to the neonate, it is essential to be able to predict the amount of drug presented to the neonate following chronic administration via milk. As noted below, it is even more crucial to understand the relationship between this amount of drug presented to the infant and the concentration of drug at or near the site of action.

Drug exposure for the suckling newborn can be viewed from several perspectives. The milk to serum (M/S) drug concentration ratio is most readily measured and most frequently reported in the literature. Unfortunately, these studies are often conducted with a limited number of subjects or with a limited number of observations (e.g., a single time point). A more useful assessment would include assaying the milk and serum concentration following dosing to steady-state or assaying the area under the milk and serum concentration following a single dose (16,17). It should be noted that even the most accurate assessment of M/S does not measure infant exposure. As will become evident in the subsequent discussion, a high or low value for M/S is meaningless unless put into the context of other parameters (i.e., maternal dose, maternal clearance, and so forth). M/S is simply a ratio of drug concentrations, a distributional property of the forces (diffusion and active transport) governing the flux into and out of milk. The influence of the physiochemical properties and protein binding of a drug on its M/S ratio has been examined (16,20–23).

Another parameter prevalent in the literature is the implication of risk (or safety) based on the dose to which the suckling neonate is exposed in milk relative to that of the mother. If this value is less than 10%, there is an implication of safety. It should be noted that this is an assumption that has rarely been validated clinically, and the use of such an untested assumption should be approached cautiously. Recent studies have advocated a more complete study design that includes measurements of drug concentrations in infant plasma (24–26) or a surrogate endpoint of effect (27). Only a limited number of studies have actually measured infant blood levels because such studies present considerable logistical and ethical problems.

Systemic exposure can be measured or defined in a variety of ways. Exposure can be expressed simply in terms of the administered dose. However, for most situations, the pharmacological or toxicological effect of a drug is best correlated with systemic concentrations, either as the peak serum drug concentration (C_{max}), the average serum concentration of drug at steady state ($\overline{C}$), or as the area under the serum concentration vs. time profile (AUC). Under ideal conditions, the best way to measure neonatal exposure in the suckling infant is to measure serum concentrations or a suitable marker of effect or toxicity following a clinical exposure. Unfortunately, this approach is usually impractical in a clinical setting given numerous ethical and logistical issues. Hence, it is essential to develop surrogate endpoints that may reflect infant exposure. AUC and $\overline{C}$ are related to one another and are dictated by the bioavailability and systemic clearance of a drug. C_{max} is a more complex parameter that may be influenced by the rate of absorption as well as bioavailability and systemic clearance. To simplify the current analysis, systemic exposure will be expressed as $\overline{C}$.

Neonate Serum Concentration

It is most likely that any untoward effects in the newborn are the result of concentrations achieved in infant serum. In its simplest form, the average serum concentration at steady-state for the infant ($\overline{C}_{serum}^{infant}$) following any route of administration can be described by Eq. (1), which says that $\overline{C}_{serum}^{infant}$ is a function of the infant's bioavailability (F^{infant}), systemic clearance ($Cl_{systemic}^{infant}$), and dose (D^{infant}).

$$\overline{C}_{serum}^{infant} = \frac{F^{infant}}{Cl_{systemic}^{infant}}[D^{infant}] \tag{1}$$

This relationship assumes linear pharmacokinetics. As applied to the exposure of the infant to drugs in milk, the D^{infant}, infant daily dose, is related to the milk concentrations as in Eq. (2), where $\overline{C}_{milk}^{maternal}$ is the concentration of drug in milk and (V_{milk}/τ) is the volume of milk consumed per nursing interval. All of the clearance and dosing terms are standardized for body weight; hence, the milk volume term is also standardized on a body weight basis. In many cases, it may be more appropriate or useful to express (V_{milk}/τ) in terms of the amount of milk consumed per day (e.g., comparison of daily dose exposures), which would necessitate the equivalent units for the expression of $Cl_{systemic}^{infant}$.

$$\overline{C}_{serum}^{infant} = \frac{F^{infant}}{Cl_{systemic}^{infant}}\left[\overline{C}_{milk}^{maternal}\left(\frac{V_{milk}}{\tau}\right)\right] \tag{2}$$

Equation (2) is frequently written in a modified form [Eq. (3)], which now involves average serum concentration at steady-state for the mother ($\overline{C}_{serum}^{maternal}$) and the milk to serum concentration ratio (M/S).

$$\overline{C}_{serum}^{infant} = \frac{F^{infant}}{Cl_{systemic}^{infant}}\left[\overline{C}_{serum}^{maternal}\left(\frac{M}{S}\right)\left(\frac{V_{milk}}{\tau}\right)\right] \tag{3}$$

Finally, assuming linear pharmacokinetics in the mother, the $\overline{C}_{serum}^{maternal}$ can be broken down into its components, which include the maternal bioavailability ($F^{maternal}$), systemic clearance ($Cl_{systemic}^{maternal}$), and daily dose ($D^{maternal}$).

$$\overline{C}_{serum}^{infant} = \frac{F^{infant}}{Cl_{systemic}^{infant}}\left[\frac{F^{maternal}\,D^{maternal}}{Cl_{systemic}^{maternal}}\left(\frac{M}{S}\right)\left(\frac{V_{milk}}{\tau}\right)\right] \tag{4}$$

Equation (4) provides valuable insights to the contributions of the various factors contributing to serum concentrations in the infant. In order to use these concentration values to assess risk directly, there is an implicit assumption that the resulting concentrations in the newborn and infant will produce the same pharmacodynamic response in the adult. This presupposes that both the qualitative and quantitative nature of the pharmacodynamics in the infant is the same as in the adult. Exposure response relationships in the developing newborn have not been well studied (28).

Exposure Index Related to Maternal Dose

Literature reports often contain reference to the percentage of maternal dose to which the infant is exposed. Exposure index with respect to body weight normalized dose, $EI_{(Dose)}$, is a straightforward computation frequently used to gauge drug exposure. Equations (1) and (4) can be equated to one another and rearranged to yield Eq. (5), which presents the determinants for this assessment of exposure. Determinants are related to the maternal pharmacokinetics (bioavailability and systemic clearance) as well as M/S and the milk consumption rate.

$$EI_{(Dose)} = \frac{D^{infant}}{D^{maternal}} = \frac{F^{maternal}}{CL^{maternal}_{systemic}} \left(\frac{M}{S}\right) \left(\frac{V_{milk}}{\tau}\right) \qquad (5)$$

Another useful approach would be to base an exposure index on the therapeutic dose established in infants. Such an EI would allow for a comparison of exposure relative to a known exposure in the population, minimizing the concern about differences in clearance between infant and mother.

Exposure Index Related to Maternal Concentration

Although much more difficult to measure, an exposure index based on the percentage of maternal concentrations achieved $EI_{(Conc)}$ is a better estimate of exposure. Equation (6) can be derived by rearranging Eq. (3) and presents the determinants of this exposure index, which are largely a function of infant pharmacokinetics (bioavailability and systemic clearance) as well as M/S and the milk consumption rate.

$$EI_{(Conc)} = \frac{\overline{C}^{infant}_{serum}}{\overline{C}^{maternal}_{serum}} = \frac{F^{infant}}{Cl^{infant}_{systemic}} \left(\frac{M}{S}\right) \left(\frac{V_{milk}}{\tau}\right) \qquad (6)$$

Ito and Koren (29) proposed this index for expressing exposure of the infant to drugs in breast milk.

In order to apply $EI_{(Dose)}$ or $EI_{(Conc)}$ to a particular clinical situation, it is important to understand the basic assumptions and limitations of these relationships. The relationships assume steady-state conditions apply for both the mother and the infant. Clearly, this assumption is an approximation of chronic drug therapy; however, application of these indices to other clinical situations would offer some general insights into exposure. Another assumption is that the pharmacokinetics of the drug are linear in both the mother and the infant. In order to estimate $EI_{(Dose)}$, one would need to know estimates of F and $Cl_{systemic}$ for the mother, whereas $EI_{(Conc)}$ would require knowledge of these same pharmacokinetic parameters in the infant. Estimates of M/S and (V_{milk}/τ) would also be required for both exposure indices. It is unlikely that one would have specific information from a given individual, hence mean values obtained from the literature would be used. As pointed out in the discussion below, understanding the sources of inter- and intrasubject variability will be as relevant as those mean values. For example, it is unlikely the pharmacokinetics of a given drug in the lactating woman will have been reported, let alone pharmacokinetic parameters for the infant. Moreover, the dynamic changes taking place in the mother in the days after parturition and the physiologic changes occurring in the newborn during the first few months will need to be incorporated into these exposure indices.

General Considerations

It is evident from Eqs. (5) and (6) that the relative value of infant exposure is proportional to M/S. Table I illustrates this point using high, intermediate, and low M/S values. Clearly, those drugs whose M/S is larger (10.0) result in greater exposure whether assessed on a dose (normalized to body weight) or concentration basis. To minimize exposure, one obvious strategy would be to use drugs with low M/S ratios. However, these ratios alone do not establish risk or exposure. Other issues may dictate the true exposure for the infant. Likewise as the milk consumption rate (V_{milk}/τ) increases, the exposure increases as well. Typically, milk consumption rate is expressed as volume per day; however, it can be normalized to body weight by dividing by infant weight at the corresponding time. Figure 1 illustrates the time course of milk consumption rate as a function of time postpartum. The use of drugs, including ethanol and smoking, reduces the normal milk production (30) and hence might affect consumption rate.

The systemic clearance of the drug in the mother has an

Table I. Hypothetical Exposure Indices [$EI_{(Dose)}$ and $EI_{(Conc)}$] as a Function of M/S and Maternal and Infant Systemic Clearances*

Maternal clearance	M/S	Infant clearance	$EI_{(Dose)}$	$EI_{(Conc)}$
High	High	50% $Cl_{maternal}$	5.6%	11.1%
(20 ml·min^{-1}·kg^{-1})	(10)	5% $Cl_{maternal}$	5.6%	111%
	Intermediate	50% $Cl_{maternal}$	0.6%	1.1%
	(1)	5% $Cl_{maternal}$	0.6%	11%
	Low	50% $Cl_{maternal}$	0.06%	0.11%
	(0.1)	5% $Cl_{maternal}$	0.06%	1.11%
Low	High	50% $Cl_{maternal}$	556%	1111%
(0.2 ml·min^{-1}·kg^{-1})	(10)	5% $Cl_{maternal}$	556%	11111%
	Intermediate	50% $Cl_{maternal}$	55.6%	111.1%
	(1)	5% $Cl_{maternal}$	55.6%	1111%
	Low	50% $Cl_{maternal}$	5.6%	11.1%
	(0.1)	5% $Cl_{maternal}$	5.6%	111.1%

EI, exposure index; M/S, milk to serum drug concentration ratio; Cl, clearance.

* Assumes $V_{milk}/\tau_{nursing}$ = 800 ml/day or 0.11 ml·kg^{-1}·min^{-1} for a 5-kg infant. $F_{maternal}$ and $F_{neonate}$ assumed to be 1.

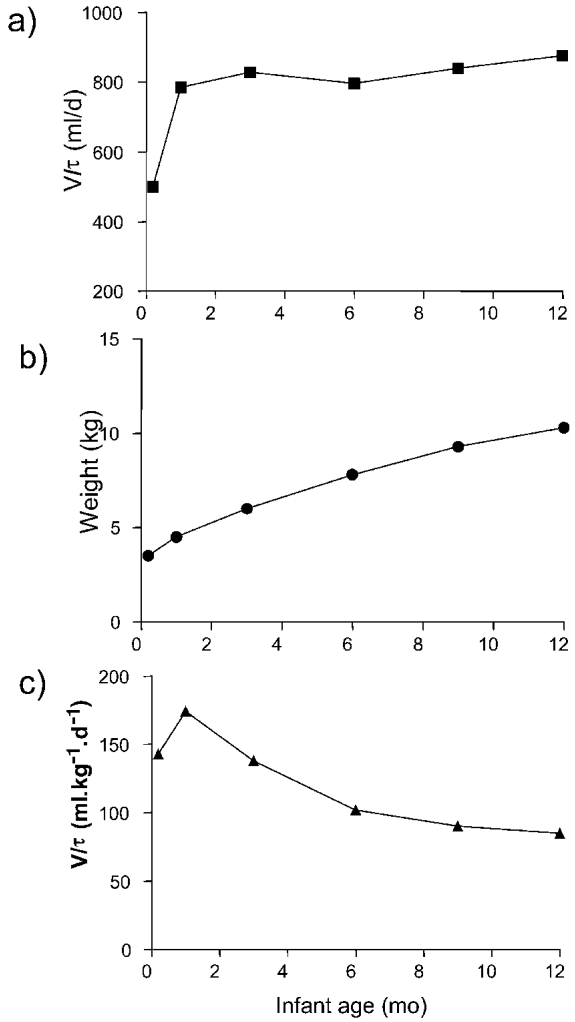

Fig. 1. Milk consumption (panel a), infant weight (panel b), and normalized milk production (panel c) as a function of infant age. Milk consumption values obtained from (126,136–138). Body weight values obtained from the CDC growth table for boys, http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/charts. htm#Set%201. Data for panel c is generated from panels a and b.

inverse relationship to the neonatal exposure as judged by the $EI_{(Dose)}$ [Eq. (4) and Table I]. The infant dose is determined by $\overline{C}_{milk}^{maternal}$ and (V_{milk}/τ). To achieve the same $\overline{C}_{milk}^{maternal}$, drugs with lower $Cl_{systemic}^{maternal}$ values require lower doses; hence, $Cl_{systemic}^{maternal}$ is inversely related to exposure based on dose. This would suggest that drugs with a lower maternal systemic clearance (e.g., due to lower intrinsic clearance or more extensive protein binding) would inherently produce greater $EI_{(Dose)}$ values compared with a drug with a higher systemic clearance and comparable M/S ratios. For any given drug, $EI_{(Dose)}$ would be higher in the case where the mother's clearance is compromised due to disease or drug–drug interaction. $EI_{(Dose)}$ would be lower in the case where the mother's fraction unbound is increased due to disease or drug–drug interaction. It should be recognized that oral bioavailability for drugs with high systemic clearance is likely to be much smaller than one. Hence, $EI_{(Dose)}$ estimates presented in Table I most likely overestimate exposure to the infant.

The systemic clearance of the drug in the infant has no influence on the neonatal exposure as judged by the $EI_{(Dose)}$ [Eq. (5) and Table I]; however, it can have a profound effect on $EI_{(Conc)}$. This would suggest that drugs with a lower neonatal systemic clearance would inherently produce greater $EI_{(Conc)}$ values compared with a drug with a higher systemic clearance and comparable M/S ratios. For a given drug, if $Cl_{systemic}^{infant}$ is diminished in a particular infant (e.g., a premature infant with poorly developed clearance pathways), then the resulting exposure is increased. $EI_{(Conc)}$ would be lower in the case where the infant's fraction unbound was increased due to lower binding protein concentration.

Specific Examples

It is clear from Table II that there are a number of drugs (carbamazepine, erythromycin, flecainide, itraconazole, metoclopramide, midazolam, omeprazole, and valproate) for which exposure [expressed as either $EI_{(Dose)}$ or $EI_{(Conc)}$] is low (<5% of maternal). Acebutolol has a high M/S ratio (5.7, Table II) and a moderately high $Cl_{systemic}^{maternal}$ resulting in a modest $EI_{(Dose)}$ projection. The $Cl_{infant}^{systemic}$ of acebutolol in 3- to 12-month-old infants is reported to be more than twice that of the adult on a body weight basis, resulting in a predicted $EI_{(Conc)}$ that would be lower than $EI_{(Dose)}$. Flecainide has a relatively high M/S ratio (2.0); however, both $Cl_{systemic}^{maternal}$ and $Cl_{systemic}^{infant}$ are reported to be high, resulting in relatively low $EI_{(Dose)}$ and $EI_{(Conc)}$ predictions. Indomethacin and lorazepam both have relatively low M/S values. However, $Cl_{infant}^{systemic}$ for these drugs in early-term infants have been reported to be 10–20% of adult values and would suggest that serum concentrations would approach 20–50% of maternal serum. Zidovudine has a low $EI_{(Dose)}$ prediction of 0.61%, but has a 10-fold higher $EI_{(Conc)}$ (Table II).

Caffeine

Caffeine illustrates several important issues with regard to exposure indices (Table III). It has a modest M/S ratio and a modest $Cl_{systemic}^{maternal}$ resulting in a relatively high $EI_{(Dose)}$. The clearance mechanism for caffeine is largely CYP1A2, a member of the CYP1A subfamily of the cytochrome P450 drug metabolizing enzymes and this pathway is induced by smoking (31). Hence, $EI_{(Dose)}$ would likely be lower in smokers compared to nonsmoking mothers (Table III). Interestingly, caffeine clearance is known to be lower in the later stages of pregnancy with women at 38 weeks having a systemic clearance of one-third of the nonsmoking adult (32). If this low $Cl_{systemic}^{maternal}$ continued postpartum, the predicted $EI_{(Dose)}$ would be greater than 40%. Fortunately, the clearance of caffeine appears to return to nonpregnant levels within the first week postpartum (32).

As noted above and illustrated in Table III, milk production (hence, milk consumption) is also lower in smokers compared to nonsmokers, which would also contribute to a lower $EI_{(Dose)}$. Milk production rate also would have an effect on $EI_{(Conc)}$ and is the source of the difference between smokers and nonsmokers in Table III for this parameter. The $Cl_{systemic}^{infant}$ in the premature newborn is less than 10% of the adult (33). This results in infant serum concentrations that would be close to adult concentrations as indicated by $EI_{(Conc)}$ of 108% (Table III). Caffeine clearance appears to approach adult levels after the end of the first year of life, and the $EI_{(Conc)}$ collapses to $EI_{(Dose)}$. As illustrated by caffeine, these exposure indices are sensitive to intersubject variability and can differ from mother to mother (e.g., variation due to smoking)

Table II. Exposure Indices [$EI_{(Dose)}$ and $EI_{(Conc)}$] for a Series of Drugs as a Function of Literature Estimates for M/S and Adult and Infant Systemic Clearances*

Drug	Exposure index (Conc)	Exposure index (Dose)	M/S	Adult Cls ($ml \cdot min^{-1} \cdot kg^{-1}$)	Infant age	Infant Cl $ml \cdot min^{-1} \cdot kg^{-1}$	M/S ref.	Adult Cl ref.	Infant Cl ref.
Acebutolol	3.70%	9.30%	5.7	6.8	3–12 mo	17.08	(70, 71)	(72)	(73)
Carbamazepine	4.05%	3.42%	0.4	1.3	Term: 1–7 d	2.22	(49, 74, 75)	(76)	(77)
Erythromycin	0.44%	0.61%	0.5	9.1	Term: 1–7 d	12.5	(78)	(79)	(80)
Flecainide	1.98%	3.96%	2	5.6	1–3 mo	11.2	(81, 82)	(83)	(84)
Indomethacin	50.50%	3.96%	0.5	1.4	Term: 7–28 d	0.11	(85, 86)	(87)	(88)
Itraconazole	1.48%	0.77%	1.6	23	3–12 mo	12.03	(89)	(90)	(91)
Lorazepam	16.70%	3.53%	0.35	1.1	Term: 1–7 d	0.23	(92, 93)	(94, 95)	(96)
Metoclopramide	1.59%	3.40%	1.9	6.2	Prem: 7–28 d	13.3	(97)	(98)	(99)
	1.92%				1–3 mo	11			(100)
Midazolam	1.34%	0.25%	0.15	6.6	Prem: 1–7 d	1.24	(101)	(102)	(103)
	1.00%				Term: 1–7 d	1.67			(104)
Omeprazole	0.12%	0.10%	0.07	7.5	3–12 mo	6.72	(105)	(106)	(107)
Theophylline	24.10%	11.10%	0.65	0.65	Prem: 1–7 d	0.3	(34, 108, 109)	(110)	(111–113)
	25.80%				Term: 1–7 d	0.28			(114)
	21.90%				Term: 7–28 d	0.33			(114, 115)
	15.00%				1–3 mo	0.48			(114)
Valproate	1.59%	3.03%	0.03	0.11	Term: 1 d	0.21	(116–118)	(119)	(120)
	1.11%				3–12 mo	0.3			(120, 121)
Zidovudine	6.39%	0.61%	1.44	26	Prem: 1 d	2.5	(89)	(122)	(123)
	6.32%				Prem: 1–7 d	2.53			(124)
	2.13%				Term: 1 d	7.5			(123)
	1.47%				Term: 1–7 d	10.9			(125)
	0.84%				Term: 7–28 d	19			(125)

M/S, milk to serum drug concentration ratio; Cl, clearance.
* Assumes $V/\tau = 800$ ml/day or 0.11 $ml \cdot kg^{-1} \cdot min^{-1}$ for a 5-kg infant. $F_{maternal}$ and $F_{neonate}$ are assumed to be 1.

and from infant to infant (e.g., ontogeny of clearance pathway).

FACTORS INFLUENCING EXPOSURE

Nursing vs. Dosing Interval

Acute Dosing

Following a single-dose administration, the timing of dose administration relative to nursing schedule can be manipulated to a limited extent. For a drug with a short half-life, the nursing mother could take the medication immediately following breast-feeding and then feed the infant on demand. For a drug with a longer half life, breast-feeding may be interrupted for a short period of time, allowing for peak maternal levels to have occurred. At the extreme, breastfeeding could be suspended for a day without a major disruption in the breast-feeding pattern provided that the mother uses a breast pump to maintain normal milk production.

Chronic Dosing

A more significant exposure is likely to occur when the mother is undergoing chronic therapy. In this situation, the

Table III. Theoretical Infant Exposure to Caffeine in Milk as Defined by $EI_{(Dose)}$ and $EI_{(Conc)}$*

	Infant				
	Premature	1–3 mo	3–5 mo	5–6 mo	Reference
Weight (kg)	1	5	8	10	
Infant Cls ($ml \cdot min^{-1} \cdot kg^{-1}$)	0.15	0.53	1.74	5.52	(33)
Mother is nonsmoker		Adult Cls($ml \cdot min^{-1} \cdot kg^{-1}$) = 1.2			(31)
$EI_{(Dose)}$ ($mg \cdot kg^{-1} \cdot d^{-1}$)	13.3%	5.4%	3.6%	2.9%	
$EI_{(Conc)}$ (ug/ml)	108%	12.3%	2.5%	0.6%	
V/τ ($ml \cdot min^{-1} \cdot kg^{-1}$)	0.20	0.08	0.05	0.04	(126)
Mother is smoker		Adult Cls ($ml \cdot min^{-1} \cdot kg^{-1}$) = 2.6			(31)
$EI_{(Dose)}$ ($mg \cdot kg^{-1} \cdot d^{-1}$)	6.1%	1.7%	1.1%	0.8%	
$EI_{(Conc)}$ (ug/ml)	108%	8.5%	1.6%	0.4%	
V/τ ($ml \cdot min^{-1} \cdot kg^{-1}$)	0.20	0.06	0.03	0.03	(126)

EI, exposure index; M/S, milk to serum drug concentration ratio; Cl, clearance.
* Literature estimates of milk consumption and systemic clearance for infants and adults together with an M/S of 0.8 were used in Eqs. (5) and (6).

decision to nurse must be framed differently. If there is reason to believe that the potential exists for serious side effects, then nursing should be suspended. If there is no overt toxicity, then any risk to the child must be balanced against the benefit of the therapy to the mother and the benefit of breast-feeding to the child.

Though optimizing the timing of the maternal dosing and infant suckling in order to minimize the infant exposure is a laudable goal, it is usually impractical. In Fig. 2, the 24-h plasma concentration time profiles for three types of drugs are depicted in relationship to a nursing scheme of once every 4 h. If one assumes a rapid equilibrium between plasma and milk (as is usually the case), the concentration profile in milk would mirror the shape of the plasma but would be displaced upward or downward depending on the M/S value. Hence, the highest exposure in terms of infant dose would coincide with peak plasma (or milk) concentrations. For drugs with a relatively short half-life that may be given 3 or more times a day, a nursing schedule that included nursing immediately preceding a given dose would minimize exposure. However, for those drugs that are administered once a day minimizing the infant exposure by timing breast-feeding in relationship to maternal dose administration appears pointless. Moreover, inter- and intrasubject variation in maternal pharmacokinetics (absorption, distribution, and elimination) as well as variation in the suckling behavior of infants would further complicate the situation and make general guidelines on the issue of timing fruitless and frustrating to patients. It would be more rational and simpler to consider the exposure in terms of an average dosing rate for drugs with longer half-life. A decision to breast-feed should be based on this average exposure rather than any complicated pharmacokinetic scheme. In that light, the aforementioned exposure indices would appear to be of considerable utility in the assessment of infant risk.

Metabolites

Another area of concern is the exposure of the infant to active (or toxic) metabolites via milk (17,19). Most of these metabolites are presumed to derive from the systemic circulation rather than being formed in mammary epithelial cells themselves (17,19). The drug metabolism capability of mammary epithelial cells is largely unknown. The presence of active metabolites may pose added drug exposure for the infant. Again, caffeine is a good example because caffeine's main metabolites (paraxanthine, theobromine, and theophylline) have considerable pharmacological activity. All of these metabolites of caffeine are present in milk and their time course follows that of plasma concentrations (34). Moreover, they possess similar M/S ratios (ranging from 0.52 to 0.82), with paraxanthine and theobromine present in comparable milk concentrations that were roughly 10 times that of theophylline (34). An estimate of total xanthine (caffeine and its three major metabolites) would result in dose exposure that is 2.5 times greater than that of caffeine alone (34).

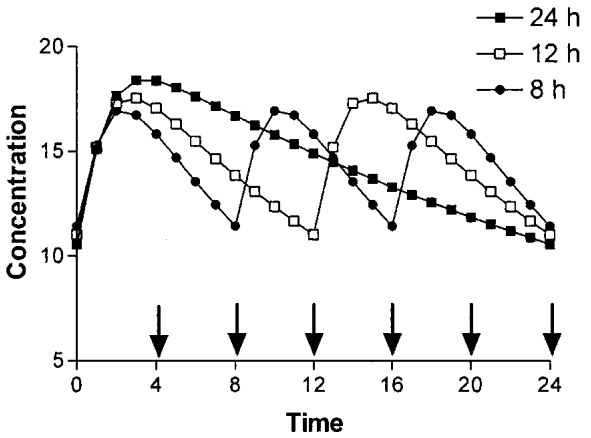

Fig. 2. Concentration vs. time course for three drugs possessing identical steady-state concentration in milk, but are dosed in different dosing intervals (once, twice and three times a day) to compensate for differences in half-lives (24, 12, and 8 h, respectively). Arrows indicate a nursing interval of every 4 h.

M/S Variability

Colostrum vs. Mature Milk

The composition and pH of colostrum (milk formed within the first few days of lactation) are different from mature milk (10,35). Colostrum tends to be produced in smaller volumes, and its pH approximates that of plasma. The total fat content is 2.9 vs. 4.2 g/dl and total protein content is 2.3 vs. 0.9 g/dl for colostrum vs. mature milk, respectively (36). Meperidine M/S ratios were found to be lower in colostrum than in mature milk (37). Morphine used as a postoperative analgesic also showed an M/S ratio of 2.45 ± 0.8 (38) for mature milk and <1 for colostrum (39). The higher M/S ratio in mature milk can be explained by partitioning of those drugs into the milk lipid content, which is greater in mature milk compared to colostrum. Thiopentone showed similar M/S ratios of <1.0 for both mature milk and colostrum (40,41). To date, there is insufficient evidence to indicate if the variability of M/S ratios from colostrum to mature milk is significant in terms of infant exposure. The clinical impact of this variability is also determined by the nature of use of the drug if it is used directly postpartum or not.

Fore- vs. Hind-Milk

Fore milk, which is the initial volume (approximately 10 ml) of milk expressed during a feeding, will have about half of the fat content compared with hind milk (later milk) (42). A group of tricyclic antidepressants (clomipramine, imipramine, amitriptyline, and dothiepin) had a gradient increase of M/S ratios from fore- to hind-milk, averaging from 1.0 in fore milk to 1.5 in hind milk (42). M/S ratios increased with the increase in fat content in fore milk and showed no correlation with fat content in hind milk (42). Paroxetine M/S ratios varied from 0.056 to 1.3 depending on the aliquot of breast milk that was assayed. Higher M/S ratios were found in hind milk (43). The same results were found for sertraline and its metabolite desmethylsertraline (44). These findings imply the greater exposure of the infant upon consuming hind milk. However, the clinical application of this observation would appear to be impractical and very limited.

Time-Dependent M/S

Wilson *et al.* (17) have described the time-dependent nature of M/S (i.e., discordance in the concentration vs. time profile of drug in milk and serum) for a number of drugs and

the implications for conducting pharmacokinetic studies to measure accurately this parameter. Though there may be consequences of a time-dependent M/S for assessing infant exposure (i.e., nursing when the ratio is lowest), interindividual variation and other practical issues (see "Nursing vs. Dosing Interval") are likely to preclude the timing of nursing to coincide with the lowest M/S ratio for a specific situation. An integrated M/S value derived from AUC measurements would appear to be of greatest utility.

Intersubject Variation in M/S

Genetic and environmental differences can manifest themselves in terms of interindividual variation in the M/S values. Intersubject variability can arise due to variation in milk pH or fat or protein content. Milk pH has been found to vary from 5.47 to 7.84 and total lipid content from 1 to 24% (45). Ionization of the drug in milk is affected by pH; in turn, the un-ionized fraction available for equilibrium with plasma varies. Lipophilic drugs would exhibit a higher M/S ratio when milk has higher lipid content. The difference in protein content may affect the binding of highly bound drugs. For example, the interpatient variability for M/S values for selective serotonin reuptake inhibitors has been reported to exhibit a coefficient of variation of 20–40%; with the range of M/S values of 0.23–1.13 (n = 14) for fluoxetine (46), 1.14–2.55 (n = 8) for sertraline (47), and 0.9–2.6 (n = 7) for citalopram (48). Coefficient of variation for anticonvulsants ranged from about 12 to 25%. M/S values (mean ± SD) have been reported for primidone (n = 12) 0.809 ± 0.09 (49), phenobarbital (n = 13) 0.36 ± 0.09 (50), and for carbamazepine (n = 16) 0.364 ± 0.087 (51).

Transporter expression was detected in lactating mammary epithelial cells for OCT1, OCT3, OCTN1, OCTN2, OATP-A, OATP-B, OATP-D, OATP-E, MRP1, MRP2, MRP5, MDR1, CNT1, CNT3, ENT1, ENT3, NCBT1, PEPT1, and PEPT2 transcripts (52). A more detailed discussion of transporters expressed in lactating mammary epithelium has been presented (53). For drugs actively transported into milk, genetic variation in transporter expression could also alter the amounts of drugs transported into milk, thus changing the M/S ratio. Cimetidine and nitrofurantoin are both actively transported into milk. M/S ratio determinations for cimetidine in 12 patients reported a mean of 5.77 and a coefficient of variation 21.5% (54). Nitrofurantoin M/S ratios showed a coefficient of variation of 43.5% (55) even though the number of subjects was small (n = 4). This wide range of variability can make it hard to determine the actual infant exposure depending on M/S values alone.

Clearance

Ontogeny of Clearance Pathways

The stage of development of clearance pathways will have substantial impact on the extent of drug exposure for the infant via milk. This is clearly delineated by the $EI_{(Conc)}$ parameter [Eq. (6)]. Alcorn and McNamara have discussed many of the issues related to the ontogeny of properties associated with pharmacokinetics in the infant (56–58). Equation (6) includes bioavailability and systemic clearance in the newborn as determinant parameters of $EI_{(Conc)}$. Bioavailability is generally reduced in the newborn, which would lower the systemic exposure in the suckling infant. It should be noted that diminished bioavailability may increase the risk of GI toxicity. Diminished systemic clearance in the infant would result in increased exposure [$EI_{(Conc)}$] and is usually the focus of concern.

One problem in attempting to use $EI_{(Conc)}$ effectively as an exposure assessment tool is the lack of information relating the clearance of the drug of interest to the specific age of the exposed infant. Ethical concerns constrain the widespread assessment of pharmacokinetics in very young children, unless there is a legitimate therapeutic use of the agent in the child. Though the intended exposure of the infant to drugs may be limited, drugs in milk could expose the infant to most prescription and OTC drugs. Moreover, a detailed examination of the pharmacokinetics of a given drug at various stages of development during the first year of life (i.e., usual lactation period) is even less likely. Alcorn and McNamara (57) have applied the classification system of Cresteil *et al.* (59) used to describe the CYP (cytochrome P450) family of drug metabolizing enzymes to all major routes of clearance in the infant (renal clearance as well as oxidative and conjugative hepatic enzymes). If this general ontological model is validated, then it might be possible to predict the changes in clearance in the infant in the absence of experimental evidence. Figure 3 illustrates the application of this approach to model $EI_{(Conc)}$ for three hypothetical drugs with numerically similar clearance values in adults, but which are governed by different clearance mechanisms. One drug has a clearance mechanism that exhibits a fetal development pattern, where the clearance pathway (on a body-weight basis) is close to that of the adult even at birth. For this type of drug, $EI_{(Conc)}$ would be low and relatively comparable to $EI_{(Dose)}$. $EI_{(Conc)}$ would change very little as the infant matures. This is a pattern one might see with drugs whose principal route of elimination is glomerular filtration or sulfation. The early neonatal profile drug would exhibit a clearance that is 25% of adult at birth (again on a body-weight basis) that reaches approximately 60% of adult values by the end of the first year of life. Substrates of CYP2D6, such as a number of antidepressants including selective serotonin reuptake inhibitors (SSRIs) (60,61), would be examples of drugs exhibiting this profile. $EI_{(Conc)}$ would track the inverse of the clearance maturation slowly diminishing as the infant reaches the first year of life (Fig. 3). The third type of drug, neonatal, has less than 5% activity or clearance relative to the adult at birth and may reach 40% of adult clearance at the end of one year (Fig. 3). Again, $EI_{(Conc)}$ would be inversely related to clearance with very high levels at birth that diminish with time. This is a pattern one might see with substrates of CYP1A2, such as caffeine (see Table III). Clearly, this is a simplified model that assumes that the patterns of clearance are the same in infants and in adults. Moreover, it assumes that all of drug clearance is associated with that one pathway. Nonetheless, it does provide insight to the relative extent of exposure for different drugs and may provide further guidance in drug selection for the lactating woman.

Transporters play an important role in drug clearance and distribution throughout the body. However, the knowledge about the ontogeny of transporters in neonates and infants is scarce (56), making it difficult to assess their role in neonatal clearance.

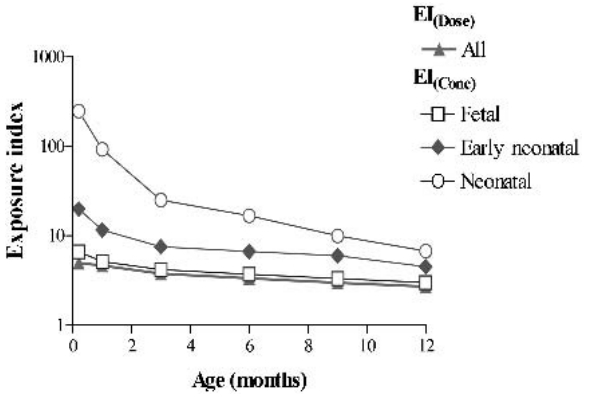

Fig. 3. Exposure indices [$\mathbf{EI}_{(Dose)}$ and $\mathbf{EI}_{(Conc)}$] as a function of infant age. Simulations assume an M/S value of 1, the milk consumption rate (V_{milk}/τ) from Fig. 1, a maternal systemic clearance ($\mathbf{Cl}^{maternal}_{systemic}$) of 2 $ml \cdot min^{-1} \cdot kg^{-1}$, and the developmental patterns (fetal, early neonatal, and neonatal) for infant systemic clearance ($\mathbf{Cl}^{infant}_{systemic}$. The developmental clearance patterns are adapted from Refs. 57 and 58 and were expressed as a fraction of adult clearance values ($ml \cdot min^{-1} \cdot kg^{-1}$). Symbols include: CYP, isoforms; ST, sulfotransferase; GST, glutathione-*S*-transferase; UGT, uridine 5′-diphosphate-glucuronosyltransferase; NAT, *N*-acetyltransferase; GFR, glomerular filtration rate; TS, tubular secretion.

Developmental pattern	Dominant Cls pathway		
	Cytochrome P450s	Phase II	Renal
Fetal	CYP3A7, CYP4A1	ST*, GST*	GFR
Early Neonatal	CYP2D6, CYP2E1	UGT*, NAT	
Neonatal	CYP3A4, CYP2C, CYP2B, CYP1A2		TS

* Isoform specific.

Pharmacogenetics

Polymorphic expression patterns for a number of drug-metabolizing enzymes (CYP2D6, CYP2C9, CYP2C19, NAT2, and others) contributes to the wide intersubject variability in the pharmacokinetics of a number of drugs (62). The impact of pharmacogenetics on drug exposure via lactation has received limited attention in the literature (63). The most well characterized polymorphic drug metabolizing enzyme is CYP2D6 (62). CYP2D6 metabolizes a large number of drugs including antidepressants, antiarrhythmics, neuroleptics, and opioids. The highly polymorphic profile of CYP2D6 has extensively been characterized (62,64).

Many of the SSRIs are substrates for both CYP2D6 and CYP2C19 (Table IV), and their use to treat depression in lactating women has received considerable attention (46–48,65–67). The role of pharmacogenetics differences on the transfer of SSRIs to the infant has not adequately been addressed. $EI_{(Conc)}$ predicted by Eq. (5) using literature estimates for M/S and adult clearance values was in good agreement with that determined in the individual studies (Table V). However, the mean data in Table V does not adequately reflect the intersubject variability. If the mother is a poor metabolizer (PM) phenotype of CYP2D6, it is likely that the $EI_{(Dose)}$ will be substantially higher than the values in Table V. If on the other hand the infant is a PM of CYP2D6, then the resulting $EI_{(Conc)}$ would likely be very much higher than that of infants that are efficient CYP2D6 metabolizers. This may be of particular concern for those SSRIs that are metabolized by CYP2D6 (fluoxetine, paroxetine, sertraline, and venlafaxine). By contrast, CYP2D6 polymorphism is likely to be less of an issue for fluvoxamine and citalopram; however, these SSRIs are predominantly metabolized by CYP2C19, which exhibits its own polymorphic pattern. Even in the most thorough of studies characterizing the SSRI transfer into infants, the number of infants is typically less than that which would be required to detect the impact of a PM on the overall clinical outcome. The deficiency of the CYP2D6 enzyme is an autosomal recessive inherited trait with 7% of Caucasians and 1% of Orientals classified as PMs (64). The incidence of CYP2C19 PMs is much higher in Asians (15–30%) than in Caucasians (3–6%) (68). The role of pharmacogenetics on drug exposure via lactation needs further consideration.

Table IV. Metabolic Pathways, Pharmacokinetic Parameters, and M/S Ratios for Selective Serotonin Reuptake Inhibitors Derived from the Literature

		Cytochrome P450 isozymes (60, 61)				Pharmacokinetics (127)			M/S	
Parent	Active metabolite	CYP2D6*†	CYP3A3/4†	CYP1A2†	CYP2C19*	Cls/F ($ml \cdot min^{-1} \cdot kg^{-1}$)	fe (%)	fu (%)	M/S	References
Citalopram		+	+		++	4.3	10.5	20	1.88	(48, 128, 129)
	Norcitalopram	++							1.80	(48)
Fluoxetine		+++	+		++	2.6	2.5	6	0.80	(24, 46, 130)
	Norfluoxetine	+++	++		++				0.59	(46)
Fluvoxamine		+	++	+++	+++	21.4	5	23	0.95	(131)
	Carboxy acid	NA	NA	NA	NA					
Paroxetine		+++	+			8.6	2	5	0.51	(66, 132, 133)
	M2 metabolite	+++								
Sertraline		++	++			38	1	2	1.90	(47, 134)
	Norsertraline	+/++							1.64	
Venlafaxine		++	+			22	4.6	73	3.03	(67, 135)
	O-desmethy venlafaxine	++							2.76	(67, 135)

M/S, milk to serum drug concentration ratio; NA, not applicable.
* Polymorphism.
† Substantial ontogeny pattern.

Table V. Dose Exposure Index [$EI_{(Dose)}$] for Selective Serotonin Reuptake Inhibitors as a Function of Literature Estimates for M/S and Adult Systemic Clearance (see Table IV)

Parent	$EI_{(Dose)}$ ($ml \cdot kg^{-1} \cdot d^{-1}$) predicted	$EI_{(Dose)}$ ($ml \cdot kg^{-1} \cdot d^{-1}$) observed	References
Citalopram	4.9%	3.2%	(48)
Fluoxetine	3.4%	3.4%	(46)
Fluvoxamine	0.5%	1.1%	(65)
Paroxetine	0.7%	1.3%	(66)
Sertraline	0.6%	0.9%	(47)
Venlafaxine	1.5%	3.5%	(67)

EI, exposure index; M/S, milk to serum drug concentration ratio. Assumes $V/\tau = 800$ ml/day or 0.11 $ml \cdot kg^{-1} \cdot min^{-1}$ for a 5-kg infant. $F_{maternal}$ is assumed to be 1.

Strategies To Minimize Exposure

Banta-Wright (13) and others have discussed approaches to minimize infant exposure and risk. Some of the proposed strategies include avoiding nonessential medication, alternative routes of administration (e.g., inhaled bronchodilaton), avoiding peak drug concentrations, maternal dosing prior to longest period of infant sleep, and other strategies (13,69).

The previous discussion of infant exposures would support other strategies that have been suggested by others as well. When selecting pharmacotherapy, consideration might be given to those agents with the following properties:

- Therapeutic window: Selecting drugs with a wide therapeutic window would likely serve to minimize adverse events in the infant.
- M/S ratio: All other factors being equal, select a drug with the lower M/S ratio. These tend to be hydrophilic anions with extensive plasma protein binding.
- Adult clearance: The greater the systemic clearance, the lower the $EI_{(Dose)}$; hence, selecting high-clearance drugs will minimize exposure.
- Ontogeny of the clearance pathway: Those agents whose clearance pathways are well developed in the infant (i.e., fetal profile). For example, those drugs that rely on glomerular filtration in the kidney or sulfation as a means of elimination.
- Pharmacogenetics of clearance pathway: Because it is unlikely that the infant will be screened for a specific genotype, those agents whose clearance is dictated largely by a polymorphic pathway (e.g., CYP2D6) should be avoided.

CONCLUSIONS

The benefits of breast-feeding for the infant and the mother are clear and compelling. The presence of drugs and other chemicals in milk can pose a dilemma for mothers and health-care workers. Virtually every drug administered to the nursing mother will find its way into the systemic circulation of the suckling infant. Hence, the question is not whether or not but how much drug is present and whether that size of exposure presents a risk to the infant. One crucial determinant of accessing risk is clearly the relative safety of the drug in question. For many drugs, the limited exposure of the infant to drug in milk is of no consequence. For others, this risk may be theoretical, but limited; and for a few drugs, such exposure may pose a significant health risk. The presence of active metabolites and the timing of nursing relative to maternal does need to be considered when addressing infant exposure. Issues of intersubject and intrasubject variation in M/S (e.g., colostrum vs. mature milk, fore- vs. hind-milk) and in infant clearance (e.g., ontogeny of elimination pathways, pharmacogenetics) play a role in modulating exposure.

In the current analysis, the relative value of expressing exposure on the basis of dose or concentration relative to maternal exposure is presented. $EI_{(Dose)}$ is largely a function of M/S and maternal systemic clearance and bioavailability, whereas $EI_{(Conc)}$ is a function of M/S and infant systemic clearance and bioavailability. $EI_{(Dose)}$ is the most readily estimated from typically available data, as maternal systemic clearance is known. However, it only reflects the amount ingested and not the actual amount reaching the systemic circulation, which is directly related to any toxic effects that might occur. It can be very useful if compared to therapeutic doses in the infant if available. $EI_{(Conc)}$ is more difficult to estimate because systemic clearance in newborns and infants is usually unknown, but it is more clinically relevant because it reflects the actual systemic concentration in the infant. More studies need to be done to estimate or predict systemic clearance in infants. Models that predict the ontogeny of clearance pathways (57) may have practical utility in estimating $EI_{(Conc)}$ for those drugs whose pharmacokinetic fate in the infant is unknown.

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REFERENCES

1. A. L. Wright. The rise of breastfeeding in the United States. *Pediatr. Clin. North Am.* **48**:1–12 (2001).
2. A. Wrightand and R. Schanler. The resurgence of breastfeeding at the end of the second millennium. *J. Nutr.* **131**:421S–425S (2001).
3. H. Vorherr. *The Breast*, Academic Press, New York, 1974.
4. J. Wilson. *Drugs in Breast Milk*, ADIS Press, Auckland, 1981.
5. R. Lawrence. *Breastfeeding*, CV Mosby, St. Louis, 1994.
6. E. L. Mortensen, K. F. Michaelsen, S. A. Sanders, and J. M. Reinisch. The association between duration of breastfeeding and adult intelligence. *JAMA* **287**:2365–2371 (2002).
7. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* **360**:187–195 (2002).
8. S. L. Hatcher. The psychological experience of nursing mothers upon learning of a toxic substance in their breast milk. *Psychiatry* **45**:172–181 (1982).
9. P. Bennet. *Drugs and Human Lactation*, Elsevier, Amsterdam, 1988.
10. P. O. Anderson. Drug use during breast-feeding. *Clin. Pharm.* **10**:594–624 (1991).
11. S. Ito. Drug therapy for breast-feeding women. *N. Engl. J. Med.* **343**:118–126 (2000).
12. C. M. Berlin Jr. Drugs and chemicals: exposure of the nursing mother. *Pediatr. Clin. North Am.* **36**:1089–1097 (1989).
13. S. A. Banta-Wright. Minimizing infant exposure to and risks from medications while breastfeeding. *J. Perinat. Neonatal. Nurs.* **11**: 71–84; quiz 85–86 (1997).
14. H. C. Atkinson, E. J. Begg, and B. A. Darlow. Drugs in human milk. Clinical pharmacokinetic considerations. *Clin. Pharmacokinet.* **14**:217–240 (1988).

15. J. T. Wilson, R. D. Brown, D. R. Cherek, J. W. Dailey, B. Hilman, P. C. Jobe, B. R. Manno, J. E. Manno, H. M. Redetzki, and J. J. Stewart. Drug excretion in human breast milk: principles, pharmacokinetics and projected consequences. *Clin. Pharmacokinet.* **5**:1–66 (1980).
16. J. T. Wilson. Determinants and consequences of drug excretion in breast milk. *Drug Metab. Rev.* **14**:619–652 (1983).
17. J. T. Wilson, R. D. Brown, J. L. Hinson, and J. W. Dailey. Pharmacokinetic pitfalls in the estimation of the breast milk/plasma ratio for drugs. *Annu. Rev. Pharmacol. Toxicol.* **25**:667–689 (1985).
18. C. M. Berlin. The excretion of drugs in human milk. *Prog. Clin. Biol. Res.* **36**:115–127 (1980).
19. C. M. Berlin Jr. Pharmacologic considerations of drug use in the lactating mother. *Obstet. Gynecol.* **58**:17S–23S (1981).
20. J. C. Fleishaker, N. Desai, and P. J. McNamara. Factors affecting the milk-to-plasma drug concentration ratio in lactating women: physical interactions with protein and fat. *J. Pharm. Sci.* **76**:189–193 (1987).
21. H. C. Atkinson and E. J. Begg. Prediction of drug distribution into human milk from physicochemical characteristics. *Clin. Pharmacokinet.* **18**:151–167 (1990).
22. S. Ito and A. Lee. Drug excretion into breast milk—overview. *Adv. Drug Deliv. Rev.* **55**:617–627 (2003).
23. J. C. Fleishaker. Models and methods for predicting drug transfer into human milk. *Adv. Drug Deliv. Rev.* **55**:643–652 (2003).
24. K. Yoshida, B. Smith, M. Craggs, and R. C. Kumar. Fluoxetine in breast-milk and developmental outcome of breast-fed infants. *Br. J. Psychiatry* **172**:175–178 (1998).
25. V. Hendrick, A. Fukuchi, L. Altshuler, M. Widawski, A. Wertheimer, and M. V. Brunhuber. Use of sertraline, paroxetine and fluvoxamine by nursing women. *Br. J. Psychiatry* **179**:163–166 (2001).
26. V. Hendrick, Z. N. Stowe, L. L. Altshuler, J. Mintz, S. Hwang, A. Hostetter, R. Suri, K. Leight, and A. Fukuchi. Fluoxetine and norfluoxetine concentrations in nursing infants and breast milk. *Biol. Psychiatry* **50**:775–782 (2001).
27. N. Epperson, K. A. Czarkowski, D. Ward-O'Brien, E. Weiss, R. Gueorguieva, P. Jatlow, and G. M. Anderson. Maternal sertraline treatment and serotonin transport in breast-feeding mother-infant pairs. *Am. J. Psychiatry* **158**:1631–1637 (2001).
28. C. M. Berlin. Sensitivity of the young infant to drug exposure through human milk. *Adv. Drug Deliv. Rev.* **55**:687–693 (2003).
29. S. Ito and G. Koren. A novel index for expressing exposure of the infant to drugs in breast milk. *Br. J. Clin. Pharmacol.* **38**:99–102 (1994).
30. M. C. Neville and C. T. Walsh. Effects of xenobiotics on milk secretion and composition. *Am. J. Clin. Nutr.* **61**:687S–694S (1995).
31. J. L. Dorne, K. Walton, and A. G. Renwick. Uncertainty factors for chemical risk assessment. Human variability in the pharmacokinetics of CYP1A2 probe substrates. *Food Chem. Toxicol.* **39**:681–696 (2001).
32. J. L. Brazier, J. Ritter, M. Berland, D. Khenfer, and G. Faucon. Pharmacokinetics of caffeine during and after pregnancy. *Dev. Pharmacol. Ther.* **6**:315–322 (1983).
33. J. V. Aranda, J. M. Collinge, R. Zinman, and G. Watters. Maturation of caffeine elimination in infancy. *Arch. Dis. Child.* **54**: 946–949 (1979).
34. C. Y. Oo, D. E. Burgio, R. C. Kuhn, N. Desai, and P. J. McNamara. Pharmacokinetics of caffeine and its demethylated metabolites in lactation: predictions of milk to serum concentration ratios. *Pharm. Res.* **12**:313–316 (1995).
35. M. C. Neville and J. Morton. Physiology and endocrine changes underlying human lactogenesis II. *J. Nutr.* **131**:3005S–3008S (2001).
36. G. M. Chan. *Lactation: the Breast-Feeding Manual for Health Professionals*, Precept, Chicago, 1997.
37. L. Borgatta, R. W. Jenny, L. Gruss, C. Ong, and D. Barad. Clinical significance of methohexital, meperidine, and diazepam in breast milk. *J. Clin. Pharmacol.* **37**:186–192 (1997).
38. V. L. Feilberg, D. Rosenborg, C. Broen Christensen, and J. V. Mogensen. Excretion of morphine in human breast milk. *Acta Anaesthesiol. Scand.* **33**:426–428 (1989).
39. N. E. Baka, F. Bayoumeu, M. J. Boutroy, and M. C. Laxenaire. Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia. *Anesth. Analg.* **94**:184–187 (2002).
40. Z. Esener, B. Sarihasan, H. Guven, and E. Ustun. Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *Br. J. Anaesth.* **69**:586–588 (1992).
41. L. W. Andersen, T. Qvist, J. Hertz, and F. Mogensen. Concentrations of thiopentone in mature breast milk and colostrum following an induction dose. *Acta Anaesthesiol. Scand.* **31**:30–32 (1987).
42. K. Yoshida, B. Smith, M. Craggs, and R. C. Kumar. Investigation of pharmacokinetics and of possible adverse effects in infants exposed to tricyclic antidepressants in breast-milk. *J. Affect. Disord.* **43**:225–237 (1997).
43. Z. N. Stowe, L. S. Cohen, A. Hostetter, J. C. Ritchie, M. J. Owens, and C. B. Nemeroff. Paroxetine in human breast milk and nursing infants. *Am. J. Psychiatry* **157**:185–189 (2000).
44. Z. N. Stowe, M. J. Owens, J. C. Landry, C. D. Kilts, T. Ely, A. Llewellyn, and C. B. Nemeroff. Sertraline and desmethylsertraline in human breast milk and nursing infants. *Am. J. Psychiatry* **154**:1255–1260 (1997).
45. M. F. Goldfarb and M. S. Savadove. Creamatocrit and pH measurements of human milk. *J. Pediatr. Gastroenterol. Nutr.* **12**: 142–143 (1991).
46. J. H. Kristensen, K. F. Ilett, L. P. Hackett, P. Yapp, M. Paech, and E. J. Begg. Distribution and excretion of fluoxetine and norfluoxetine in human milk. *Br. J. Clin. Pharmacol.* **48**:521–527 (1999).
47. J. H. Kristensen, K. F. Ilett, L. J. Dusci, L. P. Hackett, P. Yapp, R. E. Wojnar-Horton, M. J. Roberts, and M. Paech. Distribution and excretion of sertraline and N-desmethylsertraline in human milk. *Br. J. Clin. Pharmacol.* **45**:453–457 (1998).
48. J. Rampono, J. H. Kristensen, L. P. Hackett, M. Paech, R. Kohan, and K. F. Ilett. Citalopram and demethylcitalopram in human milk; distribution, excretion and effects in breast fed infants. *Br. J. Clin. Pharmacol.* **50**:263–268 (2000).
49. S. Kaneko, T. Sato, and K. Suzuki. The levels of anticonvulsants in breast milk. *Br. J. Clin. Pharmacol.* **7**:624–627 (1979).
50. W. Kuhnz, S. Koch, H. Helge, and H. Nau. Primidone and phenobarbital during lactation period in epileptic women: total and free drug serum levels in the nursed infants and their effects on neonatal behavior. *Dev. Pharmacol. Ther.* **11**:147–154 (1988).
51. W. Froescher, M. Eichelbaum, M. Niesen, K. Dietrich, and P. Rausch. Carbamazepine levels in breast milk. *Ther. Drug Monit.* **6**:266–271 (1984).
52. J. Alcorn, X. Lu, J. A. Moscow, and P. J. McNamara. Transporter gene expression in lactating and nonlactating human mammary epithelial cells using real-time reverse transcription-polymerase chain reaction. *J. Pharmacol. Exp. Ther.* **303**:487–496 (2002).
53. S. Itoand J. Alcorn. Xenobiotic transporter expression and function in the human mammary gland. *Adv. Drug Deliv. Rev.* **55**: 653–665 (2003).
54. C. Y. Oo, R. J. Kuhn, N. Desai, and P. J. McNamara. Active transport of cimetidine into human milk. *Clin. Pharmacol. Ther.* **58**:548–555 (1995).
55. P. M. Gerk, R. J. Kuhn, N. S. Desai, and P. J. McNamara. Active transport of nitrofurantoin into human milk. *Pharmacotherapy* **21**:669–675 (2001).
56. J. Alcorn and P. J. McNamara. the ontogeny of hepatic and renal systemic clearance pathways in infants: a review (part I). *Clin. Pharmacokinet.* **41**:959–998 (2002).
57. J. Alcorn and P. J. McNamara. The ontogeny of hepatic and renal systemic clearance pathways in infants: model predictions (part II). *Clin. Pharmacokinet.* 41:1077–1094 (2002).
58. J. Alcorn and P. J. McNamara. Pharmacokinetics in the newborn. *Adv. Drug Deliv. Rev.* **55**:667–686 (2003).
59. T. Cresteil. Onset of xenobiotic metabolism in children: toxicological implications. *Food Addit. Contam.* **15**:45–51 (1998).
60. S. Caccia. Metabolism of the newer antidepressants. An overview of the pharmacological and pharmacokinetic implications. *Clin. Pharmacokinet.* **34**:281–302 (1998).
61. C. Hiemke and S. Hartter. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol. Ther.* **85**:11–28 (2000).
62. H. L. McLeod and W. E. Evans. Pharmacogenomics: unlocking

the human genome for better drug therapy. *Annu. Rev. Pharmacol. Toxicol.* **41**:101–121 (2001).
63. O. Spigset and S. Hagg. Excretion of psychotropic drugs into breast milk; pharmacokinetic overview and therapeutic implications. *CNS Drugs* **9**:111–134 (1998).
64. L. Bertilsson, M. L. Dahl, P. Dalen, and A. Al-Shurbaji. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. *Br. J. Clin. Pharmacol.* **53**:111–122 (2002).
65. J. H. Kristensen, L. P. Hackett, R. Kohan, M. Paech, and K. F. Ilett. The amount of fluvoxamine in milk is unlikely to be a cause of adverse effects in breastfed infants. *J. Hum. Lact.* **18**: 139–143 (2002).
66. E. J. Begg, S. B. Duffull, D. A. Saunders, R. C. Buttimore, K. F. Ilett, L. P. Hackett, P. Yapp, and D. A. Wilson. Paroxetine in human milk. *Br. J. Clin. Pharmacol.* **48**:142–147 (1999).
67. K. F. Ilett, L. P. Hackett, L. J. Dusci, M. J. Roberts, J. H. Kristensen, M. Paech, A. Groves, and P. Yapp. Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk. *Br. J. Clin. Pharmacol.* **45**:459–462 (1998).
68. N. Poolsup, A. Li Wan Po, and T. L. Knight. Pharmacogenetics and psychopharmacotherapy. *J. Clin. Pharm. Ther.* **25**:197–220 (2000).
69. C. R. Howard and R. A. Lawrence. Drugs and breastfeeding. *Clin. Perinatol.* **26**:447–478 (1999).
70. M. J. Boutroy, G. Bianchetti, C. Dubruc, P. Vert, and P. L. Morselli. To nurse when receiving acebutolol: is it dangerous for the neonate? *Eur. J. Clin. Pharmacol.* **30**:737–739 (1986).
71. G. Bianchetti, C. Dubroc, P. Vert, M. Boutroy, and P. Morselli. Placental transfer and pharmacokinetics of acebutolol in newborn infants. *Clin. Pharmacol. Ther.* **29**:233–234 (1981).
72. B. N. Singh, W. R. Thoden, and J. Wahl. Acebutolol: a review of its pharmacology, pharmacokinetics, clinical uses, and adverse effects. *Pharmacotherapy* **6**:45–63 (1986).
73. B. J. Anderson, N. H. Holford, G. A. Woollard, and P. L. Chan. Paracetamol plasma and cerebrospinal fluid pharmacokinetics in children. *Br. J. Clin. Pharmacol.* **46**:237–243 (1998).
74. W. Kuhnz, E. Jager-Roman, D. Rating, A. Deichl, J. Kunze, H. Helge, and H. Nau. Carbamazepine and carbamazepine-10,11-epoxide during pregnancy and postnatal period in epileptic mother and their nursed infants: pharmacokinetics and clinical effects. *Pediatr Pharmacol* **3**:199–208 (1983).
75. S. Pynnonen, J. Kanto, M. Sillanpaa, and R. Erkkola. Carbamazepine: placental transport, tissue concentrations in foetus and newborn, and level in milk. *Acta Pharmacol. Toxicol. (Copenh.)* **41**:244–253 (1977).
76. L. Bertilsson and T. Tomson. Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide. An update. *Clin. Pharmacokinet.* **11**:177–198 (1986).
77. E. Rey, P. d'Athis, D. de Lauture, O. Dulac, J. Aicardi, and G. Olive. Pharmacokinetics of carbamazepine in the neonate and in the child. *Int. J. Clin. Pharmacol. Biopharm.* **17**:90–96 (1979).
78. J. Knowles. Drugs in milk. *Pediatr. Currents* **21**:28–32 (1972).
79. P. Periti, T. Mazzei, E. Mini, and A. Novelli. Clinical pharmacokinetic properties of the macrolide antibiotics. Effects of age and various pathophysiological states (part II). *Clin. Pharmacokinet.* **16**:261–282 (1989).
80. K. B. Waites, P. J. Sims, D. T. Crouse, M. H. Geerts, R. E. Shoup, W. B. Hamrick, L. B. Duffy, and G. H. Cassell. Serum concentrations of erythromycin after intravenous infusion in preterm neonates treated for ureaplasma urealyticum infection. *Pediatr. Infect. Dis. J.* **13**:287–293 (1994).
81. X. Wagner, J. Jouglard, M. Moulin, A. M. Miller, J. Petitjean, and A. Pisapia. Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am. Heart J.* **119**:700–702 (1990).
82. R. L. McQuinn, A. Pisani, S. Wafa, S. F. Chang, A. M. Miller, J. M. Frappell, G. V. Chamberlain, and A. J. Camm. Flecainide excretion in human breast milk. *Clin. Pharmacol. Ther.* **48**:262–267 (1990).
83. C. Funck-Brentano, L. Becquemont, H. K. Kroemer, K. Buhl, N. G. Knebel, M. Eichelbaum, and P. Jaillon. Variable disposition kinetics and electrocardiographic effects of flecainide during repeated dosing in humans: contribution of genetic factors, dose-dependent clearance, and interaction with amiodarone. *Clin. Pharmacol. Ther.* **55**:256–269 (1994).
84. J. A. Till, E. A. Shinebourne, E. Rowland, D. E. Ward, R. Bhamra, P. Haga, A. Johnston, and D. W. Holt. Paediatric use of flecainide in supraventricular tachycardia: clinical efficacy and pharmacokinetics. *Br. Heart J.* **62**:133–139 (1989).
85. T. H. Lebedevs, R. E. Wojnar-Horton, P. Yapp, M. J. Roberts, L. J. Dusci, L. P. Hackett, and K. F. Ilett. Excretion of indomethacin in breast milk. *Br. J. Clin. Pharmacol.* **32**:751–754 (1991).
86. O. Eeg-Olofsson, I. Malmros, C. E. Elwin, and B. Steen. Convulsions in a breast-fed infant after maternal indomethacin. *Lancet* **2**:215 (1978).
87. R. Oberbauer, P. Krivanek, and K. Turnheim. Pharmacokinetics of indomethacin in the elderly. *Clin. Pharmacokinet.* **24**:428–434 (1993).
88. M. Weninger, A. Pollak, U. Salzer-Muhar, K. A. Vergesslich, and H. R. Salzer. Pharmacokinetics of intra-arterial indomethacin treatment for patent ductus arteriosus. *Eur. J. Pediatr.* **149**: 138–140 (1989).
89. G. Briggs, R. Freeman, and S. Yaffe. *Drugs in Pregnancy and Lactation*, Williams & Wilkins, Baltimore, 1998.
90. J. Heykants, M. Michiels, W. Meuldermans, J. Monbaliu, K. Lavrijsen, A. Van Peer, J. Levran, R. Woestenbourghs, and G. Cauwenbergh. The pharmacokinetics or itraconazole in animals and man. An overview. In R. Fromtling (ed.), *Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents*, Prous Science Publisher, Barcelona, 1987.
91. L. de Repentigny, J. Ratelle, J. M. Leclerc, G. Cornu, E. M. Sokal, P. Jacqmin, and K. De Beule. Repeated-dose pharmacokinetics of an oral solution of itraconazole in infants and children. *Antimicrob. Agents Chemother.* **42**:404–408 (1998).
92. A. G. Whitelaw, A. J. Cummings, and I. R. McFadyen. Effect of maternal lorazepam on the neonate. *Br. Med. J. (Clin. Res. Ed.)* **282**:1106-8 (1981).
93. R. J. Summerfield and M. S. Nielsen. Excretion of lorazepam into breast milk. *Br. J. Anaesth.* **57**:1042–1043 (1985).
94. D. J. Greenblatt. Clinical pharmacokinetics of oxazepam and lorazepam. *Clin. Pharmacokinet.* **6**:89–105 (1981).
95. W. R. Crom, M. V. Relling, M. L. Christensen, G. K. Rivera, and W. E. Evans. Age-related differences in hepatic drug clearance in children: studies with lorazepam and antipyrine. *Clin. Pharmacol. Ther.* **50**:132–140 (1991).
96. C. A. McDermott, A. L. Kowalczyk, E. R. Schnitzler, H. H. Mangurten, K. A. Rodvold, and S. Metrick. Pharmacokinetics of lorazepam in critically ill neonates with seizures. *J. Pediatr.* **120**: 479–483 (1992).
97. A. Kauppila, P. Arvela, M. Koivisto, S. Kivinen, O. Ylikorkala, and O. Pelkonen. Metoclopramide and breast feeding: transfer into milk and the newborn. *Eur. J. Clin. Pharmacol.* **25**:819–823 (1983).
98. K. Lauritsen, L. S. Laursen, and J. Rask-Madsen. Clinical pharmacokinetics of drugs used in the treatment of gastrointestinal diseases (Part II). *Clin. Pharmacokinet.* **19**:94–125 (1990).
99. G. L. Kearns, J. N. van den Anker, M. D. Reed, and J. L. Blumer. Pharmacokinetics of metoclopramide in neonates. *J. Clin. Pharmacol.* **38**:122–128 (1998).
100. G. L. Kearns, H. L. Butler, J. K. Lane, S. H. Carchman, and G. J. Wright. Metoclopramide pharmacokinetics and pharmacodynamics in infants with gastroesophageal reflux. *J. Pediatr. Gastroenterol. Nutr.* **7**:823–829 (1988).
101. I. Matheson, P. K. Lunde, and J. E. Bredesen. Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br. J. Clin. Pharmacol.* **30**:787–793 (1990).
102. P. D. Garzone and P. D. Kroboth. Pharmacokinetics of the newer benzodiazepines. *Clin. Pharmacokinet.* **16**:337–364 (1989).
103. T. C. Lee, B. G. Charles, G. J. Harte, P. H. Gray, P. A. Steer, and V. J. Flenady. Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics. *Anesthesiology* **90**:451–457 (1999).
104. P. Burtin, E. Jacqz-Aigrain, P. Girard, R. Lenclen, J. F. Magny, P. Betremieux, C. Tehiry, L. Desplanques, and P. Mussat. Popu-

lation pharmacokinetics of midazolam neonates. *Clin. Pharmacol. Ther.* **56**:615–625 (1994).
105. J. K. Marshall, A. B. Thompson, and D. Armstrong. Omeprazole for refractory gastroesophageal reflux disease during pregnancy and lactation. *Can. J. Gastroenterol.* **12**:225–227 (1998).
106. M. Chang, G. Tybring, M. L. Dahl, E. Gotharson, M. Sagar, R. Seensalu, and L. Bertilsson. Interphenotype differences in disposition and effect on gastrin levels of omeprazole—suitability of omeprazole as a probe for CYP2C19. *Br. J. Clin. Pharmacol.* **39**:511–518 (1995).
107. E. Jacqz-Aigrain, M. Bellaich, C. Faure, J. Andre, P. Rohrlich, V. Baudouin, and J. Navarro. Pharmacokinetics of intravenous omeprazole in children. *Eur. J. Clin. Pharmacol.* **47**:181–185 (1994).
108. A. M. Yurchak and W. J. Jusko. Theophylline secretion into breast milk. *Pediatrics* **57**:518–520 (1976).
109. G. P. Stec, P. Greenberger, T. I. Ruo, T. Henthorn, Y. Morita, A. J. Atkinson Jr., and R. Patterson. Kinetics of theophylline transfer to breast milk. *Clin. Pharmacol. Ther.* **28**:404–408 (1980).
110. A. M. Taburet and B. Schmit. Pharmacokinetic optimisation of asthma treatment. *Clin. Pharmacokinet.* **26**:396–418 (1994).
111. J. V. Aranda, D. S. Sitar, W. D. Parsons, P. M. Loughnan, and A. H. Neims. Pharmacokinetic aspects of theophylline in premature newborns. *N. Engl. J. Med.* **295**:413–416 (1976).
112. J. T. Gilman, P. Gal, R. S. Levine, C. B. Hersh, and N. V. Erkan. Factors influencing theophylline disposition in 179 newborns. *Ther. Drug Monit.* **8**:4–10 (1986).
113. H. W. Ahn, W. G. Shin, K. J. Park, O. K. Suh, and J. H. Choi. Pharmacokinetics of theophylline and caffeine after intravenous administration of aminophylline to premature neonates in Korea. *Res. Commun. Mol. Pathol. Pharmacol.* **105**:105–113 (1999).
114. E. S. Moore, R. G. Faix, R. C. Banagale, and T. H. Grasela. The population pharmacokinetics of theophylline in neonates and young infants. *J. Pharmacokinet. Biopharm.* **17**:47–66 (1989).
115. D. M. Hilligoss, W. J. Jusko, J. R. Koup, and G. Giacoia. Factors affecting theophylline pharmacokinetics in premature infants with apnea. *Dev. Pharmacol. Ther.* **1**:6–15 (1980).
116. H. Nau, D. Rating, S. Koch, I. Hauser, and H. Helge. Valproic acid and its metabolites: placental transfer, neonatal pharmacokinetics, transfer via mother's milk and clinical status in neonates of epileptic mothers. *J. Pharmacol. Exp. Ther.* **219**:768–777 (1981).
117. N. Tsuru, T. Maeda, and M. Tsuruoka. Three cases of delivery under sodium valproate—placental transfer, milk transfer and probable teratogenicity of sodium valproate. *Jpn. J. Psychiatry Neurol.* **42**:89–96 (1988).
118. A. Philbert, B. Pedersen, and M. Dam. Concentration of valproate during pregnancy, in the newborn and in breast milk. *Acta Neurol. Scand.* **72**:460–463 (1985).
119. G. Zaccara, A. Messori, and F. Moroni. Clinical pharmacokinetics of valproic acid—1988. *Clin. Pharmacokinet.* **15**:367–389 (1988).
120. D. Battino, M. Estienne, and G. Avanzini. Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part I: phenobarbital, primidone, valproic acid, ethosuximide and mesuximide. *Clin. Pharmacokinet.* **29**:257–286 (1995).
121. L. Herngren, B. Lundberg, and A. Nergardh. Pharmacokinetics of total and free valproic acid during monotherapy in infants. *J. Neurol.* **238**:315–319 (1991).
122. G. D. Morse, M. J. Shelton, and A. M. O'Donnell. Comparative pharmacokinetics of antiviral nucleoside analogues. *Clin. Pharmacokinet.* **24**:101–123 (1993).
123. M. Mirochnick, E. Capparelli, and J. Connor. Pharmacokinetics of zidovudine in infants: a population analysis across studies. *Clin. Pharmacol. Ther.* **66**:16–24 (1999).
124. M. Mirochnick, E. Capparelli, W. Dankner, R. S. Sperling, R. van Dyke, and S. A. Spector. Zidovudine pharmacokinetics in premature infants exposed to human immunodeficiency virus. *Antimicrob. Agents Chemother.* **42**:808–812 (1998).
125. F. D. Boucher, J. F. Modlin, S. Weller, A. Ruff, M. Mirochnick, S. Pelton, C. Wilfert, R. McKinney Jr., M. J. Crain, M. M. Elkins, et al. Phase I evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. *J. Pediatr.* **122**:137–144 (1993).
126. J. M. Hopkinson, R. J. Schanler, J. K. Fraley, and C. Garza. Milk production by mothers of premature infants: influence of cigarette smoking. *Pediatrics* **90**:934–938 (1992).
127. K. E. Thummel and D. Shen. Appendix II, design and optimization of dosage regimens; pharmacokinetic data. In L. Goodman, L. Limbird, P. Milinoff, A. Gilman, and J. Hardman (eds), *The Pharmacological Basis of Therapeutics,* McGraw-Hill, New York, 2001, pp. 1917–2024.
128. P. N. Jensen, O. V. Olesen, A. Bertelsen, and K. Linnet. Citalopram and desmethylcitalopram concentrations in breast milk and in serum of mother and infant. *Ther. Drug Monit.* **19**:236–239 (1997).
129. O. Spigset, L. Carieborg, R. Ohman, and A. Norstrom. Excretion of citalopram in breast milk. *Br. J. Clin. Pharmacol.* **44**:295–298 (1997).
130. K. E. Isenberg. Excretion of fluoxetine in human breast milk. *J. Clin. Psychiatry* **51**:169 (1990).
131. S. Wright, S. Dawling, and J. J. Ashford. Excretion of fluvoxamine in breast milk. *Br. J. Clin. Pharmacol.* **31**:209 (1991).
132. O. Spigset, L. Carleborg, A. Norstrom, and M. Sandlund. Paroxetine level in breast milk. *J. Clin. Psychiatry* **57**:39 (1996).
133. R. Ohman, S. Hagg, L. Carleborg, and O. Spigset. Excretion of paroxetine into breast milk. *J. Clin. Psychiatry* **60**:519–523 (1999).
134. L. L. Altshuler, V. K. Burt, M. McMullen, and V. Hendrick. Breastfeeding and sertraline: a 24-hour analysis. *J. Clin. Psychiatry* **56**:243–245 (1995).
135. K. F. Ilett, J. H. Kristensen, L. P. Hackett, M. Paech, R. Kohan. and J. Rampono. Distribution of venlafaxine and its O-desmethyl metabolite in human milk and their effects in breastfed infants. *Br. J. Clin. Pharmacol.* **53**:17–22 (2002).
136. S. Rattigan, A. V. Ghisalberti, and P. E. Hartmann. Breast-milk production in Australian women. *Br. J. Nutr.* **45**:243–249 (1981).
137. N. F. Butte, C. Garza, J. E. Stuff, E. O. Smith, and B. L. Nichols. Effect of maternal diet and body composition on lactational performance. *Am. J. Clin. Nutr.* **39**:296–306 (1984).
138. M. C. Neville. Physiology of lactation. *Clin. Perinatol.* **26**:251–279 (1999).